

# Associations between Single Nucleotide Polymorphisms and Total Energy, Carbohydrate, and Fat Intakes: A Systematic Review

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## ABSTRACT

A better understanding of the genetic underpinning of total energy, carbohydrate, and fat intake is a prerequisite to develop personalized dietary recommendations. For this purpose, we systematically reviewed associations between single nucleotide polymorphisms (SNPs) and total energy, carbohydrate, and fat intakes. Four databases were searched for studies that assessed an association between SNPs and total energy, carbohydrate, and fat intakes. Screening of articles and data extraction was performed independently by 2 reviewers. Articles in English or German language, published between 1994 and September 2017, on human studies in adults and without specific populations were considered for the review. In total, 39 articles, including 86 independent loci, met the inclusion criteria. The fat mass and obesity-associated (*FTO*) gene as well as the melanocortin 4 receptor (*MC4R*) locus were most frequently studied. Limited significant evidence of an association between the *FTO* SNP rs9939609 and lower total energy intake and between the *MC4R* SNP rs17782313 and higher total energy intake was reported. Most of the other identified loci showed inconsistent results. In conclusion, there is no consistent evidence that the investigated SNPs are associated with and predictive for total energy, carbohydrate, and fat intakes. *Adv Nutr* 2018;9:425–453.

**Keywords:** genetic variant, single nucleotide polymorphism, carbohydrate intake, fat intake, energy intake, nutrigenomic

## Introduction

Overweight and obesity have become a worldwide health problem. Between 1975 and 2014, the prevalence of obesity has more than doubled (1, 2). According to the WHO, 39% of adults were overweight and 13% were obese in 2014 (3). The obesity epidemic is mainly due to the modern lifestyle, which is characterized by low physical activity and a high consumption of energy-dense food (4). However, genetic factors also

play a substantial role in the pathogenesis of obesity (5). To date, >100 loci have been identified for an association with BMI (6, 7), but the causal genetic variants and their underlying biological mechanisms are largely unknown. Furthermore, a modification of eating behaviors by genetic variants has been described (8).

In addition, studies have shown a considerable interindividual variation in metabolic responses to defined meal challenges (9, 10). This variability may be partly explained by genetic influences, and there is growing interest to better understand the gene-diet associations. The identification of associations as well as interactions between loci and dietary intake may help to elucidate the molecular pathways that link them with body weight. More research on these interactions has been recently promoted by an NIH Working Group (11). There are currently major efforts to investigate the association between genetic factors and dietary intake. For instance, loci associated with obesity are expressed in the brain (12, 13), assuming a potential role in eating behavior and food preferences. A recent genome-wide association study (GWAS) suggested that genetic variants are associated with

Supported in part by Amway GmbH, Puchheim, Germany

Author disclosures: TD, JG, and LP, no conflicts of interest. CH is a member of the scientific advisory board of 4sigma GmbH. HH is a member of scientific advisory boards of NovoNordisk, Boehringer Ingelheim, and Orexigene. Amway GmbH had no role in the design, analysis, or writing of this article.

Supplemental Material, Supplemental Table 1, Supplemental Figures 1 and 2, and Supplemental References are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/advances/>.

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Abbreviations used: BDNF, brain-derived neurotrophic factor; FGF21, fibroblast growth factor 21; FTO, fat mass and obesity associated; GWAS, genome-wide association study; LD, linkage disequilibrium; MC4R, melanocortin 4 receptor; NEGR1, neuronal growth regulator 1; PPAR $\gamma$ , PPAR  $\gamma$ ; SNP, single nucleotide polymorphism; TMEM18, transmembrane protein 18; %E, percentage of energy intake.

macronutrient consumption in observational studies (14). In addition, in 3 independent populations a gene-diet interaction on obesity has been shown for an *APOA2* polymorphism and saturated fat intake (15). In that context, most of the literature tackles the fat mass and obesity-associated (*FTO*) gene or consists of single findings from candidate gene studies without any replication. Further challenges include imprecise assessment of dietary intake, a high heterogeneity in study design, as well as the loss of standardized statistical models.

The general vision of these research activities is that genotype-based dietary recommendations may become a more effective approach for weight management and disease prevention. So far, the Food4Me project provided evidence that the personalized intervention groups lost more weight than the control group. However, integrating the information on different genetic variants into the personalized dietary recommendations had no benefit for weight loss (16, 17). Against this background, several commercially available genetic tests (direct-to-consumer tests) are currently offered with the promise to provide reliable information for better prevention or treatment of obesity and related metabolic disturbances (18). However, a strong evidence base for these tests is currently lacking.

Therefore, the aim of this study was to perform a systematic literature search to study potential associations between genetic variants and total energy, carbohydrate, and fat intakes and to provide a better knowledge base for future direct-to-consumer tests. The results will be beneficial for hypotheses of clinical trials on gene-diet interactions. They should also serve to develop more robust personalized dietary recommendations and, finally, to improve the prevention and treatment of obesity and metabolic diseases.

## Methods

This systematic review was performed according to the guidelines on systematic reviewing methodology (19) and the Preferred Reporting Items for Systematic Reviews (PRISMA) have been considered (20). This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration no. CRD42015025738).

### Search Strategy

The 4 electronic databases the Cochrane Library, Web of Science, PubMed, and Embase were searched for articles published between 1994 and September 2017. The search terms used were “genetic variant,” “gene variant,” “genotype,” “single nucleotide polymorphism,” “SNP,” “*FTO*,” “*FABP*,” “*PPARG*,” “*ADRB*,” “*APOA2*,” and “*APOA5*.” Due to biological knowledge [e.g., *PPAR*  $\gamma$  (*PPARG*) (21)] as well as due to application in direct-to-consumer tests (e.g., bodykey by NUTRILITE, Amway GmbH, Puchheim, Germany), the search terms included some selected gene names. In particular, the *FTO* locus as the genomic region with the strongest effect on body weight was specifically included in the literature search (7, 22). Furthermore, due to gene-diet interactions in clinical research studies, *APOA2* and *APOA5* were specifically

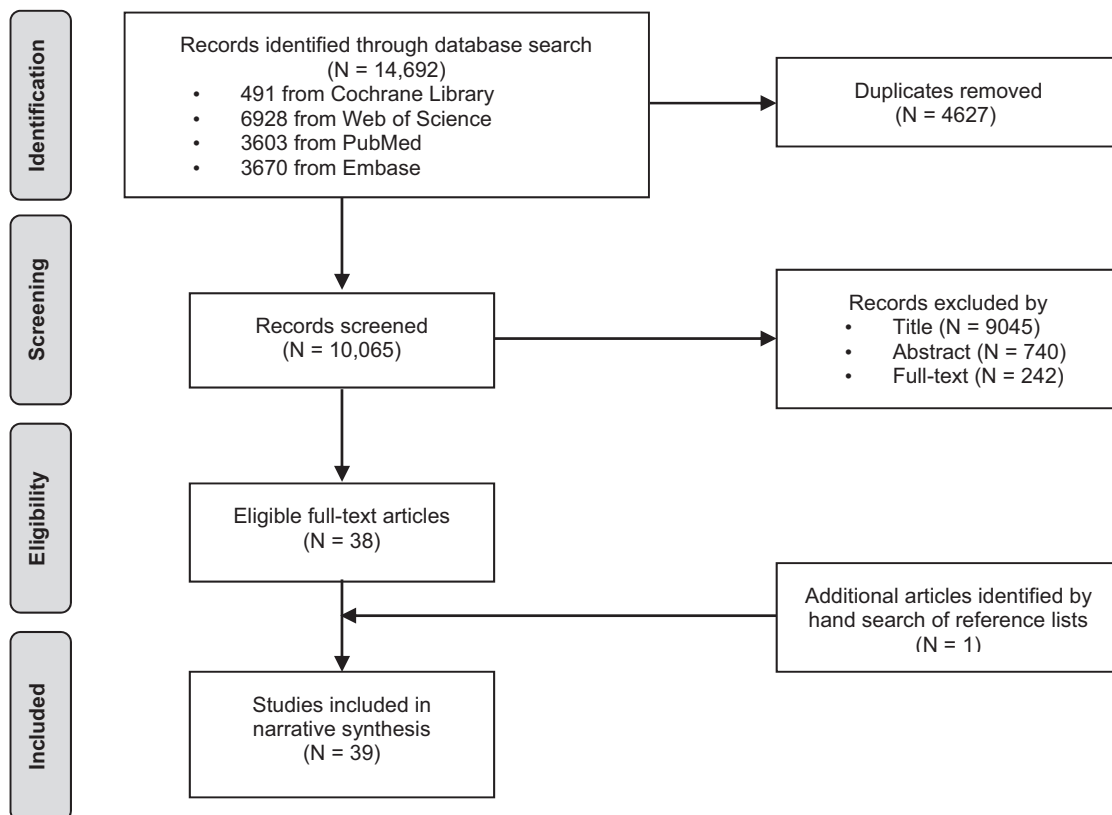
included (15). For the search strategy, the genetic terms were combined with the Boolean operator “OR.” The second search terms related to nutrition included “diet,” “energy intake,” “macronutrient intake,” “carbohydrate intake,” and “fat intake.” The nutritional search terms were combined with the Boolean operator “OR.” The genetic and nutritional search terms were combined with the Boolean operator “AND.” Depending on the database, plural forms of the search terms as well as quotation marks were used (**Supplemental Material**). Additional articles were identified through a hand-search of the reference lists of relevant publications.

### Article Screening and Selection

All of the records identified through the electronic database search were imported into the reference management software EndNote X7 (Thomsen Reuters). After the removal of duplicates, 2 independent reviewers (TD and JG) assessed titles, abstracts, and full-text articles for eligibility according to the following inclusion criteria: articles in English or German language, published between 1994 and September 2017, and in adults. Animal studies as well as studies focusing on specific populations such as pregnant or breastfeeding women or patients with cancer or other severe diseases were excluded. Furthermore, articles investigating the association between single nucleotide polymorphisms (SNPs) and the intake of food groups or the adherence to a specific diet without analyzing the association with total energy, carbohydrate, or fat intakes were not considered. Publications on copy number variations, dietary patterns, or interaction terms with no clear analysis of SNPs and energy, carbohydrate, or fat intakes were not included in this systematic review. Because protein intake accounts for fewer calories than carbohydrate and fat intakes, it has a minor contribution to energy balance. Furthermore, dietary recommendations for weight loss usually do not refer to protein intake (23, 24). Thus, protein intake was not considered. Reasons for excluding articles were documented. Throughout the article screening, discrepancies between the 2 reviewers were discussed with a third reviewer (CH). The review team contacted authors if additional information was required.

### Data Extraction

Two independent reviewers extracted the data from relevant articles into an Excel spreadsheet in order to synthesize results narratively and in a tabular form. Data extraction included the study design, study participants, intervention, primary and secondary outcomes, sample size, statistical methods, and assessment of total energy, carbohydrate, and fat intakes. Results for an association between SNPs and total energy, carbohydrate, and fat intakes were documented. Inconsistencies during data extraction were discussed with the third reviewer. Furthermore, the linkage disequilibrium (LD) based on the genotype data for the CEU population (i.e. Utah residents with Northern and Western European ancestry) was used in order to summarize and interpret findings (25, 26). LD plots for the *FTO* and *MC4R* SNPs are shown in **Supplemental Figures 1 and 2**.



**FIGURE 1** Flow chart of the systematic literature search according to Moher et al. (20).

The results were reported in a tabular synthesis, separately for each genotype according to the number of publications per single locus. In the narrative synthesis, each SNP was discussed for an association with total energy, carbohydrate, and fat intakes without quality assessment of the articles. Loci published in only 1 article are listed in **Supplemental Table 1**.

## Results

### Articles Identified

The initial database search identified 14,692 articles (**Figure 1**). Thirty-nine articles reported findings on the association between SNPs and total energy, carbohydrate, or fat intakes. These articles met the inclusion criteria according to the PICOS (Participants, Intervention, Comparator, Outcome, Study design) statement for systematic literature search (Participants: adults without severe diseases and nonpregnant or nonbreastfeeding women; Intervention: not described; Comparator: SNPs and loci; Outcome: total energy, carbohydrate, and fat intakes; Study design: all kind of studies). Twenty articles presented loci that were described only in a single study (Supplemental Table 1). SNPs that were investigated in >1 study were reviewed according to the number of articles and the analyzed SNPs.

### Characteristics of Included Studies

The publication dates of articles ranged between 2000 and 2017. More than 80% of the articles ( $n = 32$ ) represented cross-sectional, cohort, or case-control studies. Two post-prandial studies and 5 meta-analyses were included in the current review. The sample sizes ranged from 20 to 29,480 subjects and  $\leq 213,173$  individual participants in the meta-analyses. FFQs, food records, or dietary recalls were applied for the assessment of dietary intake. However, most studies ( $n = 25$ ) used FFQs. The included studies differed in terms of population characteristics such as BMI, sex distribution, disease status, and ethnicity, as well as statistical methods applied (**Tables 1–3**, Supplemental Table 1). Furthermore, *FTO* and *MC4R* SNPs differed in low and high LD values (Supplemental Figures 1 and 2).

### Gene Loci and Dietary Intake

In the following, studies considering the association between the most commonly studied loci and dietary intake are presented. **Figure 2** shows the overlap of significant associations between SNPs and total energy, carbohydrate, and fat intakes.

### *FTO* Locus and Dietary Intake

In total, 13 studies as well as 4 meta-analyses reported on potential associations between the *FTO* locus and total energy, carbohydrate, and fat intakes. Approximately 40% of these articles ( $n = 7$ ) reported results on populations of European

**TABLE 1** Association between SNPs within *FTO* locus and total energy, carbohydrate, and fat intakes<sup>1</sup>

SNP and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
rs9939609 <sup>2</sup> Case-control study	Not specified (Nigerian study)	Study in 103 people with obesity estimated as BMI ≥ 25 and 98 controls; mean age: 22.64 ± 3.6 y; mean BMI: 25.96 ± 3.1	201 (99/102)	FFQ	Energy (kcal/d)	<0.001 <sup>3</sup>	354.4 kcal/d more energy intake per risk A allele (estimated change per unit A allele β = 354.40 kcal/d)	Oyeyemi et al. (2017) (27)
Cross-sectional study	European	Mean age: 40.4 ± 13.0 y; mean BMI: 25.5 ± 4.8	1277 (536/741)	FFQ, online food habit questionnaire	Energy (kJ)	0.927 <sup>4</sup>		Livingstone et al. (2016) (28)
Systematic review and meta-analysis	White, Asian, Hispanic, African American, mixed	Mean age: 53.0 ± 9.6 y; mean BMI: 26.6 ± 2.5 (19.4–36.3)	213,173	FFQ, dietary recall, food diaries	Carbohydrate (%E)	0.959 <sup>4</sup>	Lower total energy intake in <i>FTO</i> risk genotype (β = -0.158 kcal/kg body weight per day); without adjustment: 6.46 kcal/d for each copy of the risk allele	Livingstone et al. (2015) (29)
					Fat (%E)	0.595 <sup>4</sup>		
Cross-sectional study (meta-analysis)	White, African American, Asian	Age range: 31–75 y; BMI range: 22.1–31.6	177,330 (62,275/115,055)	FFQ, dietary record, recall	Energy (kcal/d)	0.002 <sup>6</sup>	<i>FTO</i> risk allele carriers consumed less carbohydrates (β = -0.002)	Qi et al. (2014) (30)
					Fat (%E)	0.004 <sup>5</sup>		
					Carbohydrate (g/d)	0.070 <sup>7</sup>	<i>FTO</i> A risk allele associated with lower total energy intake (β = -5.9 kcal/d)	
					Carbohydrate (%E)	0.080 <sup>6</sup>		
					Fat (g/d)	0.300 <sup>7</sup>		
					Fat (%E)	0.690 <sup>6</sup>		
					Energy (kcal/d)	<0.001 <sup>6</sup>		
					Carbohydrate (g/d)	0.100 <sup>7</sup>		
					Carbohydrate (%E)	0.100 <sup>6</sup>		
					Fat (g/d)	0.440 <sup>7</sup>		
Fat (%E)	0.850 <sup>6</sup>							
Energy (kcal/d)	0.700 <sup>6</sup>							
Carbohydrate (g/d)	0.430 <sup>7</sup>							
Carbohydrate (%E)	0.770 <sup>6</sup>							
Fat (g/d)	0.680 <sup>7</sup>							
Fat (%E)	0.920 <sup>6</sup>							
Energy (kcal/d)	0.200 <sup>6</sup>							
Carbohydrate (g/d)	0.530 <sup>7</sup>							
Carbohydrate (%E)	0.530 <sup>6</sup>							
Fat (g/d)	0.320 <sup>7</sup>							
Fat (%E)	0.390 <sup>6</sup>							

**TABLE 1** (Continued)

SNP and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
Postprandial study	Not specified (English study)	Mean age: 32.1 ± 9.1 y; mean BMI: 26.8 ± 1.6	40 (40/0)	Ad libitum lunch	Energy (kJ/d)	0.335 <sup>8</sup>		Douglas et al. (2013) (31)
Cross-sectional study	Not specified (Swedish Study)	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	29,480 (11,754/17,726)	7-d menu book, FFQ	Energy (kcal/d)	0.001 <sup>9</sup>	A risk allele associated with lower total energy intake ( $\beta = -17.62$ kcal/d)	Rukh et al. (2013) (32)
Cross-sectional study	Not specified (Brazilian study)	Patients with type 2 diabetes; mean age according to genotype: TT = 57.8 ± 10.3 y, AT = 60.7 ± 12.3 y, AA = 58.3 ± 13.8 y; mean BMI according to genotype: TT = 28.8 ± 3.8, AT = 28.8 ± 4.6, AA = 29.5 ± 4.9	126 (0/126)	3-d weighed diet record	Carbohydrate (%E) Fat (%E) Energy (kJ/d)	0.220 <sup>9</sup> 0.690 <sup>9</sup> 0.629		Steemburgo et al. (2013) (33)
Cohort study	Finnish	Patients with type 2 diabetes; mean age according to genotype: TT = 59.0 ± 8.9 y, AT = 63.1 ± 7.6 y, AA = 59.9 ± 8.7 y; mean BMI according to genotype: TT = 28.3 ± 4.1, AT = 28.1 ± 3.9, AA = 28.8 ± 4.7	110 (110/0)	3-d food record	Carbohydrate (%E) Fat (%E) Energy (kJ/d)	0.409 0.019 0.047	AA genotype higher fat intake AA genotype higher energy intake	Lappalainen et al. (2012) (34)
Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Mean age of intervention group: 55.4 ± 7.2 y; mean BMI: 31.4 ± 4.6; mean age of control group: 54.9 ± 6.9 y; mean BMI: 31.0 ± 4.4	479 (160/319)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.510 <sup>10</sup> 0.650 <sup>10</sup> 0.158 <sup>11</sup>		McCaffery et al. (2012) (35)
Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Carbohydrate (%E) Fat (%E)	0.587 <sup>12</sup> 0.132 <sup>12</sup>		

**TABLE 1** (Continued)

SNP and study type		Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
Cross-sectional study	Aboriginal Canadian, Chinese, European, South Asian	Age range between 30 and 65 y	706 (351/355)	Dietary records	Energy (kcal/d)	0.045 <sup>3</sup>	Higher energy intake per minor A allele ( $\beta = 4.2$ kcal/d)	Lear et al. (2011) (36)	
					Carbohydrate (%E)	0.345 <sup>3</sup>	Lower carbohydrate intake per minor A allele ( $\beta = -2.2\%$ E)		
					Fat (%E)	0.380 <sup>3</sup>			
Aboriginal Canadian	Mean age: 45.4 $\pm$ 8.1 y; mean BMI: 29.6 $\pm$ 5.3	131 (66/65)	Dietary records	Energy (kcal/d)	0.312 <sup>3</sup>				
				Carbohydrate (%E)	0.049 <sup>3</sup>				
				Fat (%E)	0.150 <sup>3</sup>				
Chinese	Mean age: 48.0 $\pm$ 8.1 y; mean BMI: 25.7 $\pm$ 3.5	202 (92/110)	Dietary records	Energy (kcal/d)	0.457 <sup>3</sup>				
				Carbohydrate (%E)	0.440 <sup>3</sup>				
				Fat (%E)	0.322 <sup>3</sup>				
European	Mean age: 50.8 $\pm$ 9.1 y; mean BMI: 27.8 $\pm$ 5.1	184 (93/91)	Dietary records	Energy (kcal/d)	0.387 <sup>3</sup>				
				Carbohydrate (%E)	0.007 <sup>3</sup>	Higher carbohydrate intake per minor A allele ( $\beta = 2.3\%$ E)			
				Fat (%E)	0.084 <sup>3</sup>				
South Asian	Mean age: 45.0 $\pm$ 8.4 y; mean BMI: 27.9 $\pm$ 5.0	189 (100/89)	Dietary records	Energy (kcal/d)	0.438 <sup>3</sup>				
				Carbohydrate (%E)	0.188 <sup>3</sup>				
				Fat (%E)	0.187 <sup>3</sup>				
Cross-sectional study	Scottish	Mean age according to genotype: TT 43.8 $\pm$ 1.6 y, AT 43.8 $\pm$ 1.4 y, AA 43.6 $\pm$ 2.1 y; mean BMI according to genotype: TT 26.4 $\pm$ 0.9, AT 26.8 $\pm$ 0.7, AA 25.9 $\pm$ 1.2	150 (43/107)	7-d weighed food record, food diary	Energy (kJ/d)	0.024	AT/AA genotypes have higher daily energy intake (AT: 10.2 MJ/d; AA: 9.5 MJ/d) than TT genotype (9.0 MJ/d)	Speakman et al. (2008) (37)	
					Carbohydrate (%E)	0.095			
					Fat (%E)	0.024			
rs1421085 <sup>13</sup>	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 $\pm$ 10.6 y; mean BMI: 34.0 $\pm$ 6.6	3180 (1047/2133)	FFQ	Energy (kcal/d)	0.298 <sup>14</sup>		McCaferly et al. (2017) (38)	
					Carbohydrate (g/d)	0.095			
					Fat (%E)	0.024			
Cross-sectional study	Non-Hispanic white	1796 (56.5% female)	FFQ	Carbohydrate (%E)	NS				
				Fat (%E)	NS				
				Energy (kcal/d)	0.032 <sup>14</sup>	Significant higher energy intake per copy of minor allele C ( $\beta = 47.54$ kcal/d)			
					Fat (%E)	0.042 <sup>14</sup>	Nominal association between minor allele and greater fat intake ( $\beta = 0.37\%$ E)		

**TABLE 1** (Continued)

SNP and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes: mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Energy (kcal/d)	0.067 <sup>11</sup>	Each copy of the risk C allele associated with higher percentage of energy derived from fat (β = 0.522%E)	McCaffery et al. (2012) (35)
rs8050136 <sup>15</sup>					Carbohydrate (%E) Fat (%E)	0.147 <sup>12</sup> 0.019 <sup>12</sup>		
Cross-sectional study (meta-analysis)	African American, Asian American, Latino, Pacific Islander, European American, other	NA	36,973	FFQ, 24-h dietary recall	Energy (kcal/d)	0.380 <sup>16</sup>		Park et al. (2013) (39)
					Carbohydrate (%E) Fat (%E) Energy (kcal/d)	<0.001 <sup>16</sup> <0.001 <sup>16</sup> 0.900 <sup>16</sup>	Lower carbohydrate intake per-allele change (A allele) (β = -0.2796%E) Higher fat intake per-allele change (A allele) (β = 0.2244%E)	
	African American, Asian American, Latino, Pacific Islander, European American (MEC)	Mean age: 68 y (62–74 y); mean BMI: 26.1 (23.6–29.2)	19,529 (10,096/9433)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.005 <sup>16</sup> 0.003 <sup>16</sup> 0.030 <sup>16</sup>	Lower carbohydrate intake per-allele change (A allele) (β = -0.2624%E) Higher fat intake per-allele change (A allele) (β = 0.2206%E) Lower energy intake per-allele change (β = -0.0103 kcal/d)	
	African American, European American (CALICO-ARIC)	Mean age: 54 y (49–59 y); mean BMI: 26.4 (23.7–29.8)	11,114 (4957/6157)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.003 <sup>16</sup> 0.020 <sup>16</sup> 0.140 <sup>16</sup>	Lower carbohydrate intake per-allele change (β = -0.3716%E) Higher fat intake per-allele change (β = 0.2071%E)	
	African American, Latino, European American (EAGLE-NHANES II)	Mean age: 36 y (23–56 y); mean BMI: 25.7 (22.3–29.8)	6347 (2767/3580)	24-h dietary recall	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.610 <sup>16</sup> 0.070 <sup>16</sup>		

**TABLE 1** (Continued)

SNP and study type		Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
Cross-sectional study	German		Nondiabetic participants; mean age according to genotype: CC = 40 ± 1 y, CA = 42 ± 1 y, AA = 38 ± 1 y; mean BMI according to genotype: CC = 27.0 ± 0.4, CA = 28.4 ± 0.4, AA = 29.0 ± 0.9	151 (58/93)	Food diary	Energy (kcal/d)	0.010 <sup>17</sup>	C allele revealed lower energy intake compared with subjects with the minor A allele	Haupt et al. (2009) (40)
rs10163409	Meta-analysis	European ancestry	NA	71,326	FFQ	Carbohydrate (%E) Fat (%E)	0.650 <sup>17</sup> 0.600 <sup>17</sup>		
Discovery-cohort: DietGen: population-based study (n = 3 cohorts)			Type 2 diabetes cases and controls; HPEs: mean age range: 48.7–56.4 y; mean BMI range: 25.3–27.6; NHS: mean age range: 52.0–56.1 y; mean BMI range: 24.0–27.8; WGHs: mean age: 54.7 y; mean BMI: 25.9	33,355 (4076/29,455)	FFQ	Carbohydrate (%E)	0.001 <sup>18</sup>	Genetic variant associated with higher carbohydrate intake (β = 0.166%E)	Chu et al. (2013) (41)
Recovery-cohort: CHARGE (n = 12 cohorts)			NA	38,360		Fat (%E)	<0.001 <sup>18</sup>	Genetic variant associated with lower fat intake (β = -0.22%E)	
rs3751812 <sup>19</sup>	Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Energy (kcal/d)	0.066 <sup>11</sup>		McCaffery et al. (2012) (35)
rs922708 <sup>20</sup>	Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.276 <sup>12</sup> 0.054 <sup>12</sup> 0.068 <sup>11</sup>		
rs9935401 <sup>21</sup>	Cross-sectional study	German	Mean age: 49.4 ± 14.0 y; mean BMI: 27.0 ± 4.5	12,462 (6271/6191)	FFQ	Carbohydrate (%E) Fat (%E) Carbohydrate (score) Fat (score)	0.778 <sup>12</sup> 0.264 <sup>12</sup> 0.690 <sup>22</sup> 0.910 <sup>22</sup>		Holzappel et al. (2010) (42)



**TABLE 1** (Continued)

SNP and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
rs1121980	Dutch	Mean age: 57.2 ± 6.1 y; mean BMI: 25.9 ± 4.0	1 700 (0/1700)	FFQ	Energy (kcal/d)	0.200		Bauer et al. (2009) (43)
study					Carbohydrate (g/d)	0.080 <sup>23</sup>		
					Fat (g/d)	0.120 <sup>23</sup>		

<sup>1</sup> Values are means ± SDs unless otherwise indicated; in Haupt et al., values are means ± SEMs. BMI unit: kg/m<sup>2</sup>. Main results of studies concerning the association between *FTO* and total energy, carbohydrate, and fat intakes are shown. SNPs are sorted by number of publications and publication date. Details in the table are stated as mentioned in the main article. Some SNPs are in a high LD ( $r^2 > 0.8$ ) to each other. The LD values described by  $r^2$  were calculated by using a Web-tool (25); the LD plot is shown in Supplemental Figure 1. CALICO: ARIC, Causal Variants Across the Life Course and Atherosclerosis Risk in Communities Study Consortium; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium; EAGLE, Epidemiologic Architecture for Genes Linked to Environment; *FTO*, fat mass and obesity associated; GWAS, genome-wide association study; HPFS, Health Professionals Follow-Up Study; LD, linkage disequilibrium; MEC, Multi-Ethnic Cohort; NA, not available (*P* values/statistics not shown); NHS, Nurses' Health Study; ref, reference; SNP, single nucleotide polymorphism; WGHs, Women in Global Health Study; %E, percentage of energy.

<sup>2</sup>  $r^2$  to rs1421085 = 0.90;  $r^2$  to rs8050136 = 1.00;  $r^2$  to rs3751812 = 1.00;  $r^2$  to rs9922708 = 0.84;  $r^2$  to rs9935401 = 1.00;  $r^2$  to rs1121980 = 0.81.

<sup>3</sup> Adjusted for age and sex.

<sup>4</sup> Adjusted for age, sex, physical activity, BMI, country, and smoking status.

<sup>5</sup> Adjusted for body weight.

<sup>6</sup> Adjusted for age, geographical region (if available), physical activity (if available), eigenvectors (GWAS data only), and BMI.

<sup>7</sup> Adjusted for age, geographical region (if available), physical activity (if available), eigenvectors (GWAS data only), total energy intake, and BMI.

<sup>8</sup> Adjusted for age, BMI, baseline appetite scores, visit, and treatment.

<sup>9</sup> Adjusted for age, sex, season, and diet assessment method (values for carbohydrate and fat intake are additionally adjusted for energy).

<sup>10</sup> Adjusted for age, sex, and energy intake.

<sup>11</sup> Adjusted for age, sex, study site, population stratification, and weight.

<sup>12</sup> Adjusted for age, sex, study site, and population stratification.

<sup>13</sup>  $r^2$  to rs8050136 = 0.90;  $r^2$  to rs3751812 = 0.90;  $r^2$  to rs9922708 = 0.81;  $r^2$  to rs9935401 = 0.90;  $r^2$  to rs112190 = 0.91.

<sup>14</sup> Adjusted for age, sex, study site, weight, and principal components reflecting genetic ancestry.

<sup>15</sup>  $r^2$  to rs3751812 = 1.00;  $r^2$  to rs9922708 = 0.84;  $r^2$  to rs9935401 = 1.00;  $r^2$  to rs1121980 = 0.81.

<sup>16</sup> Adjusted for age at blood draw, sex, and race/ethnicity.

<sup>17</sup> Adjusted for sex, age, and BMI.

<sup>18</sup> Adjusted for age, sex (CHARGE), location, subpopulation stratification, and BMI.

<sup>19</sup>  $r^2$  to rs9922708 = 0.84;  $r^2$  to rs9935401 = 1.00;  $r^2$  to rs1121980 = 0.81.

<sup>20</sup>  $r^2$  to rs9935401 = 0.84;  $r^2$  to rs1121980 = 0.90.

<sup>21</sup>  $r^2$  to rs1121980 = 0.81.

<sup>22</sup> Adjusted for age, sex, and survey.

<sup>23</sup> Adjusted for energy.

**TABLE 2** Association between SNPs within the *MC4R* gene locus and total energy, carbohydrate, and fat intakes<sup>1</sup>

SNP and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
rs1778231 <sup>2,3</sup> Cross-sectional study	Not specified (Iranian study)	Mean age according to genotype: TT = 43.5 ± 12.4 y; CT = 45.7 ± 13.0 y; CC = 42.4 ± 12.1 y	374 (170/204)	3-d food record	Energy (kcal/d)	<0.001 <sup>3</sup>	CC genotype higher energy intake than TT (β = 217.7 kcal/d)	Khaliltehrani et al. (2015) (44)
		BMI < 25	155 (71/84)		Carbohydrate (g/d)	<0.001 <sup>4</sup>	CC genotype lower carbohydrate intake than TT (β = -29.99 g/d)	
		BMI ≥ 25	219 (99/120)		Fat (g/d)	0.200 <sup>4</sup>		
					Energy (kcal/d)	0.860 <sup>3</sup>		
					Carbohydrate (g/d)	0.040 <sup>4</sup>	CC genotype lower carbohydrate intake than TT (β = -17.56 g/d)	
					Fat (g/d)	0.090 <sup>4</sup>		
					Energy (kcal/d)	<0.001 <sup>3</sup>	CC genotype higher energy intake than TT (β = 379.8 kcal/d)	
					Carbohydrate (g/d)	<0.001 <sup>4</sup>	CC genotype lower carbohydrate intake than TT (β = -39.11 g/d)	
Cross-sectional study (meta-analysis)	White, African American, Asian	Age range: 31–75 y; BMI range: 22.1–31.6	177,330 (62,275/115,055)	FFQ, dietary record, recall	Fat (g/d)	0.730 <sup>4</sup>		Qi et al. (2014) (30)
					Energy (kcal/d)	0.660 <sup>5</sup>		
					Carbohydrate (%E)	0.590 <sup>5</sup>		
					Fat (%E)	0.080 <sup>5</sup>		Douglas et al. (2013) (31)
					Energy (k/d)	0.473 <sup>6</sup>		
Postprandial study	Not specified (English study)	Mean age: 32.1 ± 9.1 y; mean BMI: 26.8 ± 1.6	40 (40/0)	Ad libitum lunch	Energy (kcal/d)	0.830 <sup>7</sup>		
Cross-sectional study (meta-analysis)	African American, Asian American, Latino, Pacific Islander, European American, other	NA	36,973	FFQ, 24-h dietary recall	Energy (kcal/d)			Park et al. (2013) (39)
					Carbohydrate (%E)	0.800 <sup>7</sup>		
					Fat (%E)	0.460 <sup>7</sup>		
					Energy (kcal/d)	NS		
					Carbohydrate (%E)			
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					Fat (%E)			

**TABLE 2** (Continued)

SNP and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
	African American, Latino, European American (EAGLE-NHANES III)	Mean age: 54 y (49–59 y); mean BMI: 26.4 (23.7–29.8)	6347 (2767/3580)	24-h recall	Energy (kcal/d)	NS		
Cross-sectional study	Not specified (Swedish study)	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	29,480 (11,754/17,726)	7-d menu book, FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.580 <sup>8</sup>		Rukh et al. (2013) (32)
Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.680 <sup>8</sup> 0.990 <sup>8</sup> 0.684 <sup>9</sup>		McCaffery et al. (2012) (35)
Cross-sectional study	Dutch	Mean age: 57.2 ± 6.1 y; mean BMI: 25.9 ± 4.0	1700 (0/1700)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.974 <sup>10</sup> 0.910 <sup>10</sup> 0.480		Bauer et al. (2009) (43)
Cohort study	White (European ancestry)	Mean age: 54.1 ± 6.7 y	5724 (0/5724)	FFQ	Carbohydrate (g/d) Fat (g/d) Energy (kcal/d)	0.390 <sup>11</sup> 0.780 <sup>11</sup> 0.009 <sup>12</sup>	CC genotype had higher total energy intake than TT genotype (β = 84 kcal/d)	Qi et al. (2008) (45)
rs17700633	Dutch	Mean age: 57.2 ± 6.1 y; mean BMI: 25.9 ± 4.0	1700 (0/1700)	FFQ	Carbohydrate (g/d) Carbohydrate (%E) Fat (g/d)	0.110 <sup>12</sup> 0.450 <sup>12</sup> 0.001 <sup>12</sup>	CC genotype had higher total fat intake than TT genotype (β = 4.6 g/d)	Bauer et al. (2009) (43)
Cohort study	White (European ancestry)	Severe obesity; mean age: 44.3 ± 11.4 y; mean BMI: 46.0 ± 7.6	5724 (0/5724)	FFQ	Energy (kcal/d) Carbohydrate (g/d) Fat (g/d)	0.830 0.940 <sup>11</sup> 0.830 <sup>11</sup> NS		Qi et al. (2008) (45)
rs17700144	German	Mean age: 49.4 ± 14.0 y; mean BMI: 27.0 ± 4.5	12,462 (6271/6191)	FFQ	Carbohydrate (g/d) Carbohydrate (%) Fat (g/d) Fat (%)	NS NS NS NS		Holzapfel et al. (2010) (42)
Cross-sectional study	German	Mean age: 49.4 ± 14.0 y; mean BMI: 27.0 ± 4.5	12,462 (6271/6191)	FFQ	Carbohydrate (score) Fat (score)	0.190 <sup>13</sup> 0.950 <sup>13</sup>		

**TABLE 2** (Continued)

SNP and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
rs2229616 Cross-sectional study	Not specified (white persons from Utah)	Severe obesity, mean age: 44.3 ± 11.4 y; mean BMI: 46.0 ± 7.6	1029 (191/838)	FFQ	Energy (kcal/d)	0.830 <sup>14</sup>		Pichler et al. (2008) (46)
rs571312 Cross-sectional study	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Carbohydrate (g/d)  Fat (g/d)  Energy (kcal/d)	0.010 <sup>15</sup>  0.130 <sup>16</sup>  0.018 <sup>17</sup>	Carriers of the variant showed higher carbohydrate intakes than did homozygote wild-type carriers (57 g/d)  Greater total caloric intake per copy minor T allele ( $\beta = 58.84$ kcal/d)	McCaferly et al. (2017) (38)
	Non-Hispanic white		1796 (56.5% female)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.172 <sup>17</sup>		

<sup>1</sup> Values are means ± SDs unless otherwise indicated. BMI unit: kg/m<sup>2</sup>. Main results of studies concerning the association between *MC4R* and total energy, carbohydrate, and fat intakes are shown. SNPs are sorted by number of publications and publication date. Details in the table are stated as mentioned in the article. Some SNPs are in a high LD ( $r^2 > 0.8$ ) to each other. The LD values described by  $r^2$  were calculated by using a Web tool (25); the LD plot is shown in Supplemental Figure 2. CALICO: Causal Variants Across the Life Course and Atherosclerosis Risk in Communities Study Consortium; EAGLE, Epidemiologic Architecture for Genes Linked to Environment; GWAS, genomewide association study; LD, linkage disequilibrium; *MC4R*, melanocortin 4 receptor; MEC, Multi-Ethnic Cohort; NA, not available; ref, reference; SNP, single nucleotide polymorphism; %E, percentage of energy.

<sup>2</sup>  $r^2$  to rs571312 = 0.96.

<sup>3</sup> Adjusted for age, sex, physical activity, and smoking status.

<sup>4</sup> Adjusted for age, sex, physical activity, smoking status, and energy intake.

<sup>5</sup> Adjusted for age, geographical region (if available), physical activity (if available), and eigenvectors (GWAS data only).

<sup>6</sup> Adjusted for age, BMI, baseline appetite scores, visit, and treatment.

<sup>7</sup> Adjusted for age at blood draw, sex, and race/ethnicity.

<sup>8</sup> Adjusted for age, sex, season, and diet assessment method (values for carbohydrate and fat intake are additionally adjusted for energy).

<sup>9</sup> Adjusted for age, sex, study site, population stratification, and weight.

<sup>10</sup> Adjusted for age, sex, study site, and population stratification.

<sup>11</sup> Adjusted for energy.

<sup>12</sup> Adjusted for age, BMI, and diabetes status.

<sup>13</sup> Adjusted for age, sex, and survey.

<sup>14</sup> Adjusted for age, sex, and carbohydrate intake.

<sup>15</sup> Adjusted for age, sex, and BMI.

<sup>16</sup> Adjusted for age and sex.

<sup>17</sup> Adjusted for age, sex, study site, weight, and principal components reflecting genetic ancestry.

**TABLE 3** Association between SNPs within other loci and total energy, carbohydrate, and fat intakes<sup>1</sup>

Gene locus, SNP, and study type	Study characteristics according to methods and results sections			Dietary assessment	Dietary data	P	Results	First author (year) (ref)
	Study population	n (M/F)	n (M/F)					
BDNF rs6265 <sup>2</sup> Cross-sectional study (meta-analysis)	African American, Asian American, Latino, Pacific Islander, European American, other	NA	36,973	FFQ, 24-h dietary recall	Energy (kcal/d)	0.650 <sup>3</sup>		Park et al. (2013) (39)
Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.190 <sup>3</sup> 0.920 <sup>3</sup> 0.007 <sup>4</sup>	GG genotype consumed on average > 100 kcal/d more than did carriers of the less common genotypes (β = -103.37 kcal/d)	McCaffery et al. (2012) (35)
rs2030323 <sup>6</sup> Cross-sectional study	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Energy (kcal/d)	0.006 <sup>7</sup>	Fewer total caloric intake per copy minor T allele (β = -96.75 kcal/d)	McCaffery et al. (2017) (38)
rs4923461 <sup>8</sup> Cross-sectional study	Non-Hispanic white	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	1796 (56.5% female)	7-d menu book, FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS <0.001 <sup>7</sup>	Fewer total caloric intake per copy minor T allele (β = -140.49 kcal/d)	Rukh et al. (2013) (32)
rs10767664 <sup>10</sup> Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Energy (kcal/d) Carbohydrate (%E) Fat (%E)	0.360 <sup>9</sup> 0.670 <sup>9</sup> 0.830 <sup>9</sup>	AA genotype consumed on average > 100 kcal/d more than did carriers of the less common genotypes (β = -103.10 kcal/d)	McCaffery et al. (2012) (35)
rs1401635 <sup>11</sup> Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.389 <sup>5</sup> 0.289 <sup>5</sup> 0.359 <sup>4</sup>		McCaffery et al. (2012) (35)
					Carbohydrate (%E) Fat (%E)	0.354 <sup>5</sup> 0.321 <sup>5</sup>		McCaffery et al. (2012) (35)

**TABLE 3** (Continued)

Gene locus, SNP, and study type		Study characteristics according to methods and results sections			Study population		Dietary assessment		Dietary data	P	Results	First author (year) (ref)
		Mean age: 57.2 ± 6.1 y; mean BMI: 25.9 ± 4.0	n (M/F)									
rs1488830	Cross-sectional study	Dutch	1700 (0/1700)	FFQ				Energy (kcal/d)	0.580		Bauer et al. (2009) (43)	
rs925946	Cross-sectional study	Dutch	1700 (0/1700)	FFQ				Carbohydrate (g/d) Fat (g/d)	0.910 <sup>12</sup> 0.580 <sup>12</sup>		Bauer et al. (2009) (43)	
TMEM18	Cross-sectional study (meta-analysis)	African American, Asian American, Latino, Pacific Islander, European American, other	36,973	FFQ, 24-h dietary recall	NA			Energy (kcal/d)	0.330 <sup>3</sup>		Park et al. (2013) (39)	
rs6548238 <sup>13</sup>	Cross-sectional study	Not specified (Swedish study)	29,480 (11,754/17,726)	7-d menu book, FFQ	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1			Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.260 <sup>3</sup> 0.170 <sup>3</sup> 0.580 <sup>9</sup>		Rukh et al. (2013) (32)	
	Cross-sectional study	German	12,462 (6271/6191)	FFQ	Mean age: 49.4 ± 14.0 y; mean BMI: 27.0 ± 4.5			Carbohydrate (%E) Fat (%E) Carbohydrate (score) Fat (score)	0.390 <sup>9</sup> 0.092 <sup>9</sup> 0.320 <sup>14</sup> 0.030 <sup>14</sup>		Holzappel et al. (2010) (42)	
	Cross-sectional study	Dutch	1700 (0/1700)	FFQ	Mean age: 57.2 ± 6.1 y; mean BMI: 25.9 ± 4.0			Energy (kcal/d)	0.670	Trend toward an association with fat score (OR = 1.081)	Bauer et al. (2009) (43)	
rs2867125	Cross-sectional study	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	3180 (1047/2133)	FFQ	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6			Carbohydrate (g/d) Fat (g/d) Energy (kcal/d)	0.730 <sup>12</sup> 0.310 <sup>12</sup> 0.094 <sup>7</sup>		McCaffery et al. (2017) (38)	
		Non-Hispanic white	1796 (56.5% female)	FFQ				Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.349 <sup>7</sup>			

**TABLE 3** (Continued)

Gene locus, SNP, and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
<i>KCTD15</i> rs29941	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Energy (kcal/d)	0.502 <sup>7</sup>		McCaffery et al. (2017) (38)
	Non-Hispanic White		1796 (56.5% female)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.618 <sup>7</sup>		
	Not specified (Swedish study)	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	29,480 (11,754/17,726)	7-d menu book, FFQ	Energy (kcal/d)	0.860 <sup>9</sup>		Rukh et al. (2013) (32)
rs11084753 <sup>15</sup>	African American, Asian American, Latino, Pacific Islander, European American, other	NA	36,973	FFQ, 24-h dietary recall	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.950 <sup>9</sup> 0.980 <sup>9</sup> 0.820 <sup>3</sup>		Park et al. (2013) (39)
	German	Mean age: 49.4 ± 14.0 y; mean BMI: 27.0 ± 4.5	12,462 (6271/6191)	FFQ	Carbohydrate (%E) Fat (%E) Carbohydrate (score) Fat (score)	0.730 <sup>3</sup> 0.630 <sup>3</sup> 0.160 <sup>14</sup> 0.030 <sup>14</sup>	Trend toward an association with fat score (OR = 1.066)	Holzapfel et al. (2010) (42)
rs368794	Dutch	Mean age: 57.2 ± 6.1 y; mean BMI: 25.9 ± 4.0	1700 (0/1700)	FFQ	Energy (kcal/d)	0.640		Bauer et al. (2009) (43)
	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Carbohydrate (g/d) Fat (g/d) Energy (kcal/d)	0.020 <sup>12</sup> 0.110 <sup>12</sup> 0.078 <sup>7</sup>	Carriers of the risk T allele ate more total carbohydrates (per allele effect: 2.50 g/d)	McCaffery et al. (2017) (38)
<i>NEGR1</i> rs2815752 <sup>16</sup>	Non-Hispanic white		1796 (56.5% female)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.042 <sup>7</sup>	Higher total caloric intake per copy minor C allele (β = 39.58 kcal/d)	

**TABLE 3** (Continued)

Gene locus, SNP, and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
Cross-sectional study (meta-analysis)	African American, Asian American, Latino, Pacific Islander, European American, other	NA	36,973	FFQ, 24-h dietary recall	Energy (kcal/d)	0.170 <sup>3</sup>		Park et al. (2013) (39)
Cross-sectional study	Not specified (Swedish study)	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	29,480 (11,754/17,726)	7-d menu book, FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	0.610 <sup>3</sup> 0.130 <sup>3</sup> 0.004 <sup>9</sup>	Obesity-risk T allele associated with lower total energy intake (β = -12.15 kcal/d) Obesity-risk T allele associated with higher carbohydrate intake (β = 0.23%E) Obesity-risk T allele associated with lower fat intake (β = -0.21%E)	Rukh et al. (2013) (32)
rs10789336 <sup>17</sup> Cross-sectional study	German	Mean age: 49.4 ± 14.0 y; mean BMI: 27.0 ± 4.5	12,462 (6271/6191)	FFQ	Carbohydrate (score) Fat (score)	0.220 <sup>14</sup> 0.960 <sup>14</sup>		Holzapfel et al. (2010) (42)
rs2568958 Cross-sectional study	Dutch	Mean age: 57.2 ± 6.1 y; mean BMI: 25.9 ± 4.0	1700 (0/1700)	FFQ	Energy (kcal/d) Carbohydrate (g/d) Fat (g/d)	0.900 0.490 <sup>12</sup> 0.120 <sup>12</sup>		Bauer et al. (2009) (43)
SH2B1 rs7498665 <sup>18</sup> Cross-sectional study	Not specified (Swedish study)	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	29,480 (11,754/17,726)	7-d menu book, FFQ	Energy (kcal/d) Carbohydrate (%E) Fat (%E) Carbohydrate (score) Fat (score)	0.850 <sup>9</sup> 0.800 <sup>9</sup> 0.490 <sup>9</sup> 0.460 <sup>14</sup> 0.350 <sup>14</sup>		Rukh et al. (2013) (32)
Cross-sectional study	German	Mean age: 49.4 ± 14.0 y; mean BMI: 27.0 ± 4.5	12,462 (6271/6191)	FFQ	Energy (kcal/d) Carbohydrate (g/d) Fat (g/d)	0.550 0.340 <sup>12</sup> 0.003 <sup>12</sup>		Holzapfel et al. (2010) (42)
Cross-sectional study	Dutch	Mean age: 57.2 ± 6.1 y; mean BMI: 25.9 ± 4.0	1700 (0/1700)	FFQ	Carbohydrate (g/d) Fat (g/d)		Risk G allele associated with increased total fat intake (per allele effect: 1.08 g/d)	Bauer et al. (2009) (43)



**TABLE 3** (Continued)

Gene locus, SNP, and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
rs7359397 <sup>19</sup>								
Cross-sectional study	Diverse racial and ethnic groups	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Energy (kcal/d)	0.568 <sup>7</sup>		McCaffery et al. (2017) (38)
					Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.452 <sup>7</sup>		
rs4788099	Non-Hispanic white		1796 (56.5% female)	FFQ	Energy (kcal/d)	0.398 <sup>4</sup>		McCaffery et al. (2012) (35)
Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Energy (kcal/d)	0.398 <sup>4</sup>		
MTCH2								
rs10838738 <sup>20</sup>	Not specified (Swedish study)	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	29,480 (11,754/17,726)	7-d menu book, FFQ	Carbohydrate (%E) Fat (%E)	0.742 <sup>5</sup> 0.845 <sup>5</sup>		Rukh et al. (2013) (32)
Cross-sectional study					Energy (kcal/d)	0.410 <sup>9</sup>		
					Carbohydrate (%E) Fat (%E) Carbohydrate (score) Fat (score) Energy (kcal/d)	0.750 <sup>9</sup> 0.570 <sup>9</sup> 0.470 <sup>14</sup> 0.540 <sup>14</sup> 0.890		Holzappel et al. (2010) (42)
	German	Mean age: 49.38 ± 13.97; mean BMI: 26.97 ± 4.49	12,462 (6271/6191)	FFQ	Carbohydrate (g/d) Fat (g/d)	0.740 <sup>12</sup> 0.380 <sup>12</sup>		Bauer et al. (2009) (43)
Cross-sectional study	Dutch	Mean age: 57.2 ± 6.1 y; mean BMI: 25.9 ± 4.0	1700 (0/1700)	FFQ	Energy (kcal/d)	0.936 <sup>7</sup>		McCaffery et al. (2017) (38)
rs3817334								
Cross-sectional study	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Energy (kcal/d)	0.936 <sup>7</sup>		McCaffery et al. (2017) (38)
ETV5/SFRS10								
rs7647305	Non-Hispanic white		1796 (56.5% female)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.462 <sup>7</sup>		
Cross-sectional study	Not specified (Swedish study)	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	29,480 (11,754/17,726)	7-d menu book, FFQ	Energy (kcal/d)	0.280 <sup>9</sup>		Rukh et al. (2013) (32)
					Carbohydrate (%E) Fat (%E)	0.540 <sup>9</sup> 0.870 <sup>9</sup>		

**TABLE 3** (Continued)

Gene locus, SNP, and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
Cross-sectional study	Dutch	Mean age: 57.2 ± 6.1 y; mean BMI: 25.9 ± 4.0	1700 (0/1700)	FFQ	Energy (kcal/d)	0.820		Bauer et al. (2009) (43)
rs9816226					Carbohydrate (g/d)	0.520 <sup>12</sup>		
					Fat (g/d)	0.970 <sup>12</sup>		
Cross-sectional study	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Energy (kcal/d)	0.112 <sup>7</sup>		McCaffery et al. (2017) (38)
GNPDA2					Carbohydrate (%E)	NS		
					Fat (%E)	NS		
					Energy (kcal/d)	0.013 <sup>7</sup>	Higher total caloric intake per copy minor A allele (β = 86.85 kcal/d)	
rs10938397 <sup>21</sup>								
Cross-sectional study	Not specified (Swedish study)	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	29,480 (11,754/17,726)	7-d menu book, FFQ	Energy (kcal/d)	0.039 <sup>9</sup>	Obesity-risk G allele associated with lower total energy intake (β = -10.97 kcal/d)	Rukh et al. (2013) (32)
					Carbohydrate (%E)	0.700 <sup>9</sup>		
					Fat (%E)	0.840 <sup>9</sup>		
					Energy (kcal/d)	0.370		Bauer et al. (2009) (43)
					Carbohydrate (g/d)	0.790 <sup>12</sup>		
					Fat (g/d)	0.630 <sup>12</sup>		
rs12641981					Energy (kcal/d)	0.559 <sup>7</sup>		McCaffery et al. (2017) (38)
Cross-sectional study	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Carbohydrate (%E)	NS		
					Fat (%E)	NS		
					Energy (kcal/d)	0.606 <sup>7</sup>		
					Carbohydrate (g/d)			
					Fat (g/d)			
FGF21					Carbohydrate (%E)			
					Fat (%E)			
					Energy (kcal/d)			
rs838133 <sup>22</sup>					Carbohydrate (%E)			
Meta-analysis	European ancestry	NA	71,326	FFQ	Carbohydrate (%E)	<0.001 <sup>23</sup>	Genetic variant associated with increased carbohydrate intake (β = 0.23%E)	Chu et al. (2013) (41)
					Fat (%E)	<0.001 <sup>23</sup>	Genetic variant associated with decreased fat intake (β = -0.21%E)	

**TABLE 3** (Continued)

Gene locus, SNP, and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
rs838147 Meta-analysis	Multi-ethnic			FFQ	Carbohydrate (%E)	<0.001 <sup>24</sup>	Minor allele associated with higher carbohydrate intake ( $\beta = 0.25\%$ E)	Tanaka et al. (2013) (14)
GWA cohort (CHARGE)	Multi-ethnic		37,537			<0.001 <sup>24</sup>	Minor allele associated with higher carbohydrate intake ( $\beta = 0.30\%$ E)	
Replication cohort (DietGen) PPAR $\alpha$	US population-based cohorts		33,533			0.006 <sup>24</sup>	Minor allele associated with higher carbohydrate intake ( $\beta = 0.18\%$ E)	
rs1801282 Cross-sectional study	White	Mean age according to sex: women = 38.3 $\pm$ 11.7 y, men = 37.5 $\pm$ 10.7 y; mean BMI according to sex: women = 27.3 $\pm$ 6.0, men = 28.6 $\pm$ 5.4	700 (290/410)	FFQ	Energy (kcal/d)	0.810 <sup>25</sup>		Bouchard-Mercier et al. (2012) (47)
Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 $\pm$ 7.2 y; mean BMI: 36.3 $\pm$ 6.1	2075 (912/1163)	FFQ	Fat (g/d)	0.040 <sup>26</sup>	Ala12 carriers had higher total fat intake than Pro12/Pro12 carriers	
					Fat (%E)	0.030 <sup>25</sup>	Ala12 carriers had higher relative fat intake than Pro12/Pro12 carriers	McCaffery et al. (2012) (35)
BCDIN3D/FAIM2 rs7138803 Cross-sectional study	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 $\pm$ 10.6 y; mean BMI: 34.0 $\pm$ 6.6	3180 (1047/2133)	FFQ	Energy (kcal/d)	0.343 <sup>7</sup>		McCaffery et al. (2017) (38)
	Non-Hispanic white		1796 (56.5% female)	FFQ	Carbohydrate (%E)	NS		
	Not specified (Swedish study)	Mean age: 58.0 $\pm$ 7.6 y; mean BMI: 25.8 $\pm$ 4.1	29,480 (11,754/17,726)	7-d menu book, FFQ	Fat (%E)	NS		
					Energy (kcal/d)	0.648 <sup>7</sup>		
					Energy (kcal/d)	0.960 <sup>9</sup>		Rukh et al. (2013) (32)
CBI-R/CNR-1 rs1049353 Cross-sectional study	Not specified (Spanish study)	Mean age: 45.8 $\pm$ 11.3 y; mean BMI: 36.9 $\pm$ 6.1	896 (0/896)	3-d food record	Carbohydrate (%E)	0.570 <sup>9</sup>		
					Fat (%E)	0.640 <sup>9</sup>		
					Energy (kcal/d)	NS		de Luis et al. (2016) (48)
					Carbohydrate (g/d)	NS		
					Fat (g/d)	NS		

**TABLE 3** (Continued)

Gene locus, SNP, and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
Cross-sectional study	Not specified (Italian study)	Elderly subjects; mean age according to genotype: GG = 69.7 ± 3.4 y; AA/AG = 70.4 ± 3.2 y; mean BMI according to genotype: GG = 28.9 ± 5.7, AA/AG = 27.8 ± 6.4	118 (60/58)	FFQ	Carbohydrate (g/d)	0.150 <sup>27</sup>		Caruso et al. (2012) (49)
CD36 rs1761667 Cross-sectional study	White, African, West Asian, East Asian	Two age groups: AGE-1, 18–29 y; AGE-2, 30–55 y; mean BMI: 22.9 ± 0.3	136 (41/95)	FFQ, 3-d food diary	Energy (kcal/d)	NS		Shen et al. (2017) (50)
Cross-sectional study	Mestizos	Normal-weight subjects; mean age: 40.2 ± 15.1 y; mean BMI: 22.4 ± 1.9	132 (68/64)	3-d food record	Fat (g/d) Energy (kcal/d)	NS 0.160		Ramos-Lopez et al. (2015) (51)
MAP2K5 rs2241423 <sup>28</sup> Cross-sectional study	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Overweight subjects; mean age: 43.2 ± 13.9 y; mean BMI: 27.5 ± 1.4	163 (78/85)		Carbohydrate (g/d)	0.100	AA genotype had higher intake of calories than the other genotypes	
					Fat (g/d)	0.380		
					Energy (kcal/d)	<0.001		
					Carbohydrate (g/d)	0.070		
		Obese subjects; mean age: 42.5 ± 12.4 y; mean BMI: 34.5 ± 4.6	146 (56/90)		Fat (g/d)	<0.001	AA genotype had higher intake of total fat than the other genotypes	
		Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Energy (kcal/d)	0.906 <sup>7</sup>		McCaifery et al. (2017) (38)
	Non-Hispanic white		1796 (56.5% female)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.907 <sup>7</sup>		

**TABLE 3** (Continued)

Gene locus, SNP, and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
rs2241420 Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Energy (kcal/d)	0.621 <sup>4</sup>		McCaffery et al. (2012) (35)
<i>MTIF3</i> rs1885988 <sup>29</sup> Cross-sectional study	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Energy (kcal/d)	0.637 <sup>7</sup>		McCaffery et al. (2017) (38)
rs7988412 Cross-sectional study	Non-Hispanic white		1796 (56.5% female)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.485 <sup>7</sup>		
<i>QPCTL/GIPR</i> rs2287019 Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Energy (kcal/d)	0.995 <sup>4</sup>		McCaffery et al. (2012) (35)
					Carbohydrate (%E) Fat (%E)	0.932 <sup>5</sup> 0.832 <sup>5</sup>		
					Energy (kcal/d)	0.951 <sup>7</sup>		McCaffery et al. (2017) (38)
					Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.726 <sup>7</sup>		

**TABLE 3** (Continued)

Gene locus, SNP, and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
rs11672660 Cross-sectional study	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Energy (kcal/d)	0.383 <sup>4</sup>		McCaffery et al. (2012) (35)
SEC16B/RASAL2 rs543874 <sup>30</sup> Cross-sectional study	Diverse racial and ethnic groups (non-Hispanic white, African American, Hispanic, Asian/Pacific Islander, American Indian)	Participants with impaired glucose tolerance and at high risk of diabetes; mean age: 50.8 ± 10.6 y; mean BMI: 34.0 ± 6.6	3180 (1047/2133)	FFQ	Energy (kcal/d)	0.910 <sup>7</sup>		McCaffery et al. (2017) (38)
rs10913469 Cross-sectional study	Non-Hispanic white	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	29,480 (11,754/17,726)	FFQ	Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.639 <sup>7</sup>		
TNN3K rs1514175 <sup>31</sup> Cross-sectional study	Not specified (Swedish study)	Mean age: 58.0 ± 7.6 y; mean BMI: 25.8 ± 4.1	29,480 (11,754/17,726)	7-d menu book, FFQ	Energy (kcal/d)	0.800 <sup>9</sup>		Rukh et al. (2013) (32)
					Carbohydrate (%E) Fat (%E)	0.710 <sup>9</sup> 0.750 <sup>9</sup>		
					Energy (kcal/d)	0.827 <sup>7</sup>		McCaffery et al. (2017) (38)
					Carbohydrate (%E) Fat (%E) Energy (kcal/d)	NS NS 0.450 <sup>7</sup>		

**TABLE 3** (Continued)

Gene locus, SNP, and study type	Study population	Study characteristics according to methods and results sections	n (M/F)	Dietary assessment	Dietary data	P	Results	First author (year) (ref)
rs1514176	African American, American Indian/Alaska Native, Asian/Pacific Islander, white, other	Patients with type 2 diabetes; mean age: 57.6 ± 7.2 y; mean BMI: 36.3 ± 6.1	2075 (912/1163)	FFQ	Energy (kcal/d)	0.097 <sup>4</sup>		McCaffery et al. (2012) (35)
					Carbohydrate (%E) Fat (%E)	0.978 <sup>5</sup> 0.111 <sup>5</sup>		

<sup>1</sup> Values are means ± SDs unless otherwise indicated. BMI unit: kg/m<sup>2</sup>. Main results of studies concerning the association between gene loci and total energy, carbohydrate, and fat intakes are shown. SNPs are sorted by number of publications and publication date. Details in the table are stated as mentioned in the article. Some SNPs are in a high LD ( $r^2 > 0.8$ ) to each other. The LD values described by  $r^2$  were calculated by using a Web tool (25). *BCDN3D/FAIM2*, *BCDN3* domain containing RNA methyltransferase/Fas apoptotic inhibitory molecule 2; *BDNF*, brain-derived neurotrophic factor; *CB1R/CNR1*, cannabinoid receptor 1; *CD36*, CD36 molecule; *CHARGE*, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium; *ETV5/SFR510*, ETS variant 5; *FGF21*, fibroblast growth factor 21; *GNPDA2*, glucosamine-6-phosphate deaminase 2; *GWA*, Genome Wide Association; *KCTD15*, potassium channel tetramerization domain containing 15; *LD*, linkage disequilibrium; *MAP2K5*, mitogen-activated protein kinase 5; *MTC2*, mitochondrial carrier 2; *MITF3*, mitochondrial translational initiation factor 3; *NA*, not available; *NEGR1*, neuronal growth regulator 1; *PPARG*, PPAR  $\gamma$ ; *QPCT1/GIPR*, glutamyl-peptide cyclotransferase-like/gastric inhibitory polypeptide receptor; *RASAL2*, RAS protein activator-like 2; *ref*, reference; *SEC16B*, SEC16 homolog B; *endoplasmic reticulum export factor*; *SH2B1*, SH2B adaptor protein 1; *SNP*, single nucleotide polymorphism; *TMEM18*, transmembrane protein 18; *TNNI3K*, TNNI3 interacting kinase; %E, percentage of energy.

<sup>2</sup>  $r^2$  to rs4923461 = 0.82;  $r^2$  to rs1488830 = 0.82.

<sup>3</sup> Adjusted for age at blood draw, sex, and race/ethnicity.

<sup>4</sup> Adjusted for age, sex, study site, population stratification, and weight.

<sup>5</sup> Adjusted for age, sex, study site, and population stratification.

<sup>6</sup>  $r^2$  to rs10767664 = 1.00;  $r^2$  to rs4923461 = 0.91;  $r^2$  to rs1488830 = 0.91.

<sup>7</sup> Adjusted for age, sex, study site, weight, and principal components reflecting genetic ancestry.

<sup>8</sup>  $r^2$  to rs1488830 = 1.00;  $r^2$  to rs10767664 = 0.91.

<sup>9</sup> Adjusted for age, sex, season, and diet assessment method (values for carbohydrate and fat intake are additionally adjusted for energy).

<sup>10</sup>  $r^2$  to rs1488830 = 0.91.

<sup>11</sup>  $r^2$  to rs925946 = 1.00.

<sup>12</sup> Adjusted for energy.

<sup>13</sup>  $r^2$  to rs2867125 = 1.00.

<sup>14</sup> Adjusted for age, sex, and survey.

<sup>15</sup>  $r^2$  to rs368794 = 0.84.

<sup>16</sup>  $r^2$  to rs10789336 = 0.96;  $r^2$  to rs2568958 = 0.96.

<sup>17</sup>  $r^2$  to rs2568958 = 1.00.

<sup>18</sup>  $r^2$  to rs4788099 = 1.00;  $r^2$  to rs7359397 = 0.97.

<sup>19</sup>  $r^2$  to rs4788099 = 0.97.

<sup>20</sup>  $r^2$  to rs3817334 = 0.84.

<sup>21</sup>  $r^2$  to rs12641981 = 0.97.

<sup>22</sup>  $r^2$  to rs838147 = 0.81.

<sup>23</sup> Adjusted for age, sex (CHARGE), location, subpopulation stratification, and BMI.

<sup>24</sup> Adjusted for age, sex, study specific covariates, and BMI.

<sup>25</sup> Adjusted for age, sex, and BMI.

<sup>26</sup> Adjusted for age, sex, BMI, and energy intake.

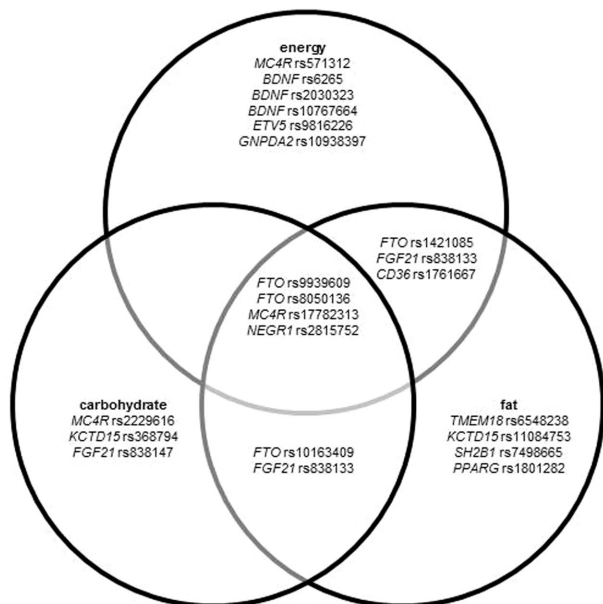
<sup>27</sup> Adjusted for age, sex, calories, and BMI.

<sup>28</sup>  $r^2$  to rs2241420 = 0.95.

<sup>29</sup>  $r^2$  to rs7988412 = 0.95.

<sup>30</sup>  $r^2$  to rs10913469 = 0.96.

<sup>31</sup>  $r^2$  to rs1514176 = 1.00.



**FIGURE 2** Venn diagram showing the overlap of significant associations ( $P < 0.05$ ) between SNPs and total energy, carbohydrate, and fat intakes. In this diagram, the statistical model used has not been considered. *BDNF*, brain-derived neurotrophic factor; *CD36*, CD36 molecule; *ETV5*, ETS variant 5; *FGF21*, fibroblast growth factor 21; *FTO*, fat mass and obesity-associated; *GNPDA2*, glucosamine-6-phosphate deaminase 2; *KCTD15*, potassium channel tetramerization domain-containing 15; *MC4R*, melanocortin 4 receptor; *NEGR1*, neuronal growth regulator 1; *PPARG*, PPAR  $\gamma$ ; *SH2B1*, SH2B adaptor protein 1; SNP, single nucleotide polymorphism; *TMEM18*, transmembrane protein 18.

ancestry. Six publications presented data for different populations (e.g., Asian, African American, American Indian, Hispanic, and Asian or Pacific Islanders). The sample sizes varied between 40 and 29,480 participants in observational and experimental studies and yielded 213,173 subjects in the meta-analyses. In total, 8 different *FTO* SNPs were investigated, whereas data for SNP rs9939609 were presented in >60% of the articles ( $n = 11$ ) (Table 1).

Three publications, including 2 meta-analyses, reported a significant association between the A risk allele of rs9939609 and lower total energy intake ( $P < 0.01$ ) (29, 30, 32). Both meta-analyses estimated a lower total energy intake of 6.4 kcal/d (unadjusted) (29) or 5.9 kcal/d (adjusted) (30), respectively. In contrast, other studies reported evidence of a significant association between the A risk allele with a higher total energy intake (27, 33, 36, 37). Four articles did not find evidence for a significant association between SNP rs9939609 and total energy intake (Table 1) (28, 31, 34, 35). In addition, an association with higher total energy intake was reported for risk allele carriers of the *FTO* SNPs rs1421085 and rs8050136, which are in a high LD to rs9939609 ( $r^2 > 0.90$ ) (38, 40), whereas Park et al. (39) observed findings in the opposite direction in African and European Americans. The SNPs rs3751812, rs9922708, and rs1121980 showed consistently nonsignificant associations with total energy intake (Table 1).

With regard to carbohydrate intake, *FTO* risk allele carriers of rs9939609 consumed fewer carbohydrates [ $\beta = -0.002\%$  of energy (%E);  $P = 0.005$ ] (29). Lear et al. (36) analyzed a sample of 706 individuals of different ethnicities for associations between rs9939609 and carbohydrate intake, resulting in nonsignificant findings. However, subanalyses suggested a lower carbohydrate intake per A allele change in Aboriginal Canadians ( $\beta = -2.2\%$ E;  $P = 0.049$ ) and a higher intake per minor A allele in participants of European descent ( $\beta = 2.3\%$ E;  $P = 0.007$ ). Park et al. (39) observed a significantly lower carbohydrate intake (in %E) per A allele change for the SNP rs8050136, whereas Haupt et al. (40) did not. In a joint analysis of samples of European ancestry ( $n = 71,326$ ), A allele carriers of the SNP rs10163409, which is not in LD to rs8050136, showed a significantly positive association with carbohydrate intake ( $\beta = 0.166\%$ E;  $P = 0.001$ ) (41). Nonsignificant results were consistently reported for the SNPs rs1421085, rs3751812, rs9922708, rs9935401, and rs1121980 and carbohydrate intake (Table 1).

With regard to fat intake, significantly positive associations between obesity-risk alleles of SNP rs9939609, rs1421085, and rs8050136 and fat intake were observed. Steemburgo et al. (33) showed a positive association between SNP rs9939609 and fat intake as percentage of energy ( $P = 0.019$ ) only for females ( $n = 126$ ). McCaffery et al. (38) confirmed this result in a subanalysis of non-Hispanic white participants, showing a nominal association between the obesity-associated minor allele of rs1421085 and greater fat intake ( $\beta = 0.37\%$ E;  $P = 0.042$ ). Moreover, Park et al. (39) described a significantly positive association between the *FTO* rs8050136 genotype and higher fat intake (Table 1). In contrast, in the meta-analysis of Livingstone et al. (29), the *FTO* risk allele carriers of rs9939609 consumed less fat ( $P = 0.004$ ). Chu et al. (41) showed a significant inverse association between the SNP rs10163409 and fat intake ( $\beta = -0.22\%$ E;  $P \leq 0.001$ ) in a subcohort of 33,531 individuals. With regard to fat intake, nonsignificant results were consistently reported for the SNPs rs3751812, rs9922708, rs9935401, and rs1121980 (Table 1).

#### Melanocortin 4 Receptor Locus and Dietary Intake

Eleven publications (8 observational studies, 1 experimental study, and 2 meta-analyses) studied associations between the melanocortin 4 receptor (*MC4R*) locus and total energy, carbohydrate, and fat intakes (Table 2). Almost one-third of the articles ( $n = 3$ ) included data from European populations. The remaining articles included data from mixed populations ( $n = 4$ ) or nonspecified individuals ( $n = 4$ ). The sample sizes varied between 40 and 29,480 individuals for observational and experimental studies and between 36,973 and 177,330 for the 2 meta-analyses. The studies reported data on 5 *MC4R* SNPs: rs17782313, rs17700633, rs17700144, rs2229616, and rs571312 (Table 2).

Most articles (8 out of 11) investigated the *MC4R* SNP rs17782313, which is in high LD to rs571312 ( $r^2 = 0.96$ ). Two of them reported a significant association between the CC genotype and a higher total energy intake ( $P < 0.01$ )



(44, 45). For SNP rs571312, a similar significantly positive association with energy intake was reported ( $\beta = 58.84$  kcal/d;  $P = 0.02$ ) (38). Other studies, including 2 meta-analyses, did not find significant associations between *MC4R* SNPs and total energy intake, or for rs17782313, rs17700633, or rs2229616 (Table 2).

With regard to carbohydrate intake, a study in an Iranian population showed a significant association between SNP rs17782313 and a lower carbohydrate intake ( $P = 0.04$  in lean subjects,  $P < 0.001$  in overweight subjects) (44). A study in persons with severe obesity showed that carriers of the rs2229616 variant 103I had a higher carbohydrate intake ( $P = 0.01$ ) (46). Other studies did not observe significant associations between SNPs rs17782313, rs17700633, rs571312, or rs17700144 and carbohydrate intake.

With regard to fat intake, results were nonsignificant, with 1 exception (Table 2). Only the analysis of 5724 white women, performed by Qi et al. (45) showed a significant association between the CC genotype and a higher total fat intake in grams per day ( $P = 0.001$ ). This association was no longer significant, when data were expressed as percentage of total energy intake.

### Other Loci and Dietary Intake

The remaining 18 loci analyzed for an association with total energy, carbohydrate, or fat intakes in >1 article are listed in Table 3. Ten cross-sectional studies and 3 meta-analyses were identified. The sample sizes varied between 118 and 71,326 participants. Data on total energy intake were available in 10 articles and data on carbohydrate and fat intakes in 11 articles.

Two studies on the brain-derived neurotrophic factor (*BDNF*) locus showed a significantly positive association between the obesity-risk alleles and total energy intake (35, 38). No significant association between *BDNF* SNPs and total energy intake was found in the other articles (32, 39, 43). With regard to carbohydrate and fat intakes, nonsignificant findings were reported for all 7 *BDNF* SNPs.

For SNP rs6548238 in the transmembrane protein 18 (*TMEM18*) locus, a significant association with fat intake ( $P = 0.030$ ) in a sample of 12,462 German adults was reported for T allele carriers (42), which was not confirmed by other studies (32, 38, 39, 43). Consistently, no significant associations were found between *TMEM18* SNPs and total energy or carbohydrate intakes.

For the potassium channel tetramerization domain-containing 15 (*KCTD15*) locus, no significant associations with total energy intake were shown (32, 38, 39, 42, 43). However, SNP rs368794 showed a significant association with higher carbohydrate intake ( $P = 0.020$ ) (43). Studies on the SNP rs11084753, which is in LD to rs368794 ( $r^2 = 0.8$ ) did not confirm this result (39, 42). With regard to fat intake and rs11084753, Park et al. (39) did not find any significant relation, whereas Holzapfel et al. (42) described a significant association with a higher fat score ( $P = 0.03$ ). Moreover, no significant associations were reported for rs29941 or for rs368794 and fat intake (32, 38, 43).

A significant association between the neuronal growth regulator 1 (*NEGR1*) SNP rs2815752 and lower total energy intake ( $P = 0.004$ ) was described in a Swedish cross-sectional study ( $n = 29,480$ ) (32). However, significance was lost after correction for misreporting. McCaffery et al. (38) confirmed the significant finding in non-Hispanic white participants. This association was not confirmed by the meta-analysis of Park et al. (39). In the Swedish study, a significant association between rs2815752 and higher carbohydrate intake ( $P \leq 0.001$ ) was reported (32). This significant result was not confirmed by the other articles (38, 39, 42, 43). With regard to fat intake, no association with *NEGR1* SNPs was described (38, 39, 42, 43), with the exception of Rukh et al. (32) who found a significantly inverse association between the rs2815752 T allele carriers and fat intake ( $\beta = -0.21\%E$ ;  $P \leq 0.001$ ) (Table 3).

None of the studies investigating the SH2B adaptor protein 1 (*SH2B1*) locus reported significant associations with total energy, carbohydrate, or fat intakes, with one exception. Bauer et al. (43) found a significantly higher fat intake for risk G allele carriers of SNP rs7498665 ( $P = 0.003$ ). The SNPs rs7647305 and rs9816226 at the ETS variant 5 (*ETV5/SFRS10*) locus (32, 38, 43) showed no significant associations with total energy, carbohydrate, or fat intakes, except for the subanalysis of McCaffery et al. (38).

The glucosamine-6-phosphate deaminase 2 (*GNPDA2*) locus was not significantly associated with total energy, carbohydrate, or fat intakes (Table 3). Only Rukh et al. (32) showed that the obesity-risk G allele was significantly associated ( $\beta = -10.97$  kcal/d;  $P = 0.039$ ) with a lower energy intake, although this result was no longer significant after correction for multiple comparisons.

Two SNPs that were in high LD ( $r^2 = 0.81$ ) at the fibroblast growth factor 21 (*FGF21*) locus were significantly associated with a higher carbohydrate intake as a percentage of energy ( $P < 0.001$ ) (14, 41). Chu et al. (41) presented data on fat intake and showed a significantly negative association with SNP rs838133 ( $\beta = -0.21\%E$ ).

For the *PPARG* SNP rs1801282, there was no significant association with total energy or carbohydrate intakes (Table 3). However, a significantly higher fat intake was observed for Ala12 carriers compared with carriers of the Pro12 allele (47). Significantly positive associations were also found for the rs1761667 at the *CD36* locus. Ramos-Lopez et al. (51) presented data showing a higher intake of calories ( $P < 0.001$ ) and a higher total fat intake ( $P < 0.001$ ) for the AA genotype of overweight participants but not for subjects with obesity. This association was not confirmed by the study of Shen et al. (50).

No significant associations between SNPs and total energy, carbohydrate, or fat intakes were found for the other loci described in Table 3.

### Discussion

The purpose of this review was to systematically explore associations between SNPs and total energy, carbohydrate, or fat intakes. In total, 39 articles, including 86 different loci and

176 SNPs, were identified. Twenty loci were described in detail in this review, and the others are listed in Supplemental Table 1.

First, significant associations were reported between the *FTO* rs9939609 and rs8050136 risk alleles and total energy intake (Table 1). One study (32) and 2 partly overlapping meta-analyses (29, 30) reported a significant association ( $P < 0.003$ ) between rs9939609 and a lower total energy intake. Considering the estimated effect sizes per risk allele of  $-6.4$  (unadjusted) and  $-5.9$  (adjusted) kcal/d from the 2 partly overlapping meta-analyses (29, 30), the results might be clinically irrelevant with respect to measurement errors in the collection of dietary data. In contrast, studies (27, 33, 36, 37) reporting a significantly higher energy intake presented unadjusted results, apart from Oyeyemi et al. (27) and Lear et al. (36) who adjusted for age and sex. Furthermore, the significant associations with higher energy intake were described in specific target groups and limited sample sizes (27, 33, 36, 37).

It must be emphasized that results were mainly obtained in cohorts of European ancestry. Qi et al. (30) replicated the significant association between rs9939609 and a lower energy intake in a subanalysis of whites, but Lear et al. (36) could not replicate a significant association after dividing participants according to ethnicity. Therefore, the significant association between *FTO* rs9939609 and energy intake observed in white populations is possibly not applicable to other ethnicities.

Moreover, the reported association with a lower energy intake was unexpected due to the association between the *FTO* locus and a higher body mass (22). In addition, a major limitation is the measurement error inherent in collecting self-reported dietary intake data (52, 53). Rukh et al. (32) indicated that the significant association between the *FTO* locus and lower energy intake became nonsignificant after excluding misreporters. Sonestedt et al. (54) analyzed the relation between *FTO* risk allele carriers and underreporting of dietary intake, showing a higher frequency of underreporters among AA carriers of the *FTO* SNP rs9939609 than among TT carriers.

However, since Frayling et al. (22) identified the association between the *FTO* locus and BMI, many studies have tried to elucidate the molecular mechanisms underlying this relation (37, 55). Recently, Claussnitzer et al. (56) identified the *FTO* SNP rs1421085 as the causal variant whose risk allele leads to an enhanced fat storage and lower mitochondrial fat burning. This latter observation suggests that the modest increase in fat storage is due to lower thermogenesis and energy expenditure rather than due to a difference in energy intake. Taken together, the association between *FTO* SNPs and a lower total energy intake is weak and possibly of low clinical relevance despite large sample sizes and sufficient statistical power. In addition, there is little biological plausibility due to the heterogeneity of reported mechanisms and, in particular, evidence that gene variants may affect energy expenditure rather than intake.

The results for an association between *FTO* SNPs and carbohydrate intake were also inconsistent. Livingstone et

al. (29) and Park et al. (39) showed a significantly lower carbohydrate intake in risk allele carriers of rs9939609 and rs8050136, respectively. Chu et al. (41) showed a higher intake for rs10163409. No significant evidence for an association between SNPs and carbohydrate intake was shown in the remaining studies ( $n = 10$ ). In addition, a subanalysis by Lear et al. (36) described a significant association between rs9939609 and a higher carbohydrate intake in a cohort of Aboriginal Canadians and a lower carbohydrate intake in European persons. This ethnic difference was not confirmed by the meta-analysis of Qi et al. (30). Therefore, there is no consistent evidence to conclude that *FTO* SNPs are associated with carbohydrate intake.

Six out of 17 articles described a significant association between *FTO* SNPs and fat intake, whereas 1 study and 1 meta-analysis reported a significantly positive association between rs9939609 and fat intake (29, 33). Consistently, a significant association between the risk C allele of rs1421085 (LD to rs9939609,  $r^2 = 0.9$ ) and a higher fat intake as a percentage of energy was reported in a mixed population (35) and in a subgroup of non-Hispanic white participants (38). Furthermore, the meta-analysis of Park et al. (39) suggests that carriers of the obesity-risk allele (C allele) of the SNP rs8050136 are characterized by a higher fat intake. Due to the high linkage between these SNPs, results suggest a positive association between the *FTO* risk allele and fat intake. However, the effect sizes were small and the changes in dietary intake across years were not considered. It is questionable whether this finding, which is largely based on epidemiologic studies, is of clinical relevance.

Second, results for an association between *MC4R* SNPs and dietary intake were inconsistent. The *MC4R* locus is known to be associated with BMI (13), eating behavior (57), and the regulation of food intake (58). Significantly positive associations with total energy intake have been shown for rs17782313 and rs571312. Khalilitehrani et al. (44) showed that, after further adjustment for energy intake, the significant association remained only in the overweight group. The same study also presented significant evidence for a negative association between rs17782313 and carbohydrate intake. The results may be ascribed to the association between *MC4R* and BMI itself. However, no other studies ( $n = 6$ ) confirmed this significant result. Furthermore, the association between a higher total fat intake and rs17782313 was no longer significant after adjustment for energy intake. Therefore, the genetic association studies identified in this review do not provide consistent evidence that the *MC4R* SNPs are significantly associated with total energy, carbohydrate, or fat intakes.

Third, associations between further loci and total energy, carbohydrate, and fat intakes were more consistent, especially in terms of nonsignificant findings. One reason could be that fewer articles, and therefore lower heterogeneity, have been published for these loci. Most of the loci (Table 3) are known to be associated with body weight management (12, 59, 60). Moreover, *BDNF* is involved in neuronal regulatory pathways of appetite and energy balance in animal studies

(61) but is also associated with BMI in humans (62). The latter might explain the consistent positive association between total energy intake and the obesity-risk genotype of *BDNF* SNPs. Significant associations between a lower energy intake and the obesity-risk allele of the SNP rs2815752 (*NEGR1*) were shown in 2 studies (32, 38). It can be supposed that the *NEGR1* as well as *TMEM18* loci, which are also associated with BMI (13), are involved in food regulation due to their function in neural development (63). As investigated by Berglund et al. (64), the *FGF21* locus is involved in carbohydrate and lipid metabolism, which may drive the positive association between *FGF21* SNPs and carbohydrate intake (14, 41).

### Strengths and Limitations

The major strength of this systematic review is that the inclusion of identified SNPs associated with total energy, carbohydrate, or fat intakes was not limited to a specific locus. This gives a wide overview of articles focusing on a direct association between SNPs and total energy, carbohydrate, and fat intakes, published between 1994 and September 2017. This strength is in direct contrast to the systematic review and meta-analysis performed by Livingstone et al. (29) who focused only on associations between *FTO* SNPs and macronutrient intake. The other 3 meta-analyses were not based on a systematic review, but on original data (30, 39, 41). A further strength is that this systematic review was not restricted to a specific study type and included experimental as well as population-based studies. However, this does not allow pooling of data in a meta-analysis. The present review did not include articles describing copy number variations, mutation analyses, haplotypes, or studies investigating the association between genetic factors and food groups or dietary patterns as well as gene-diet interactions. Furthermore, potential associations between SNPs and protein intake, which plays a minor role in the treatment and prevention of overweight and obesity (23, 24), were not considered. It must be mentioned that GWASs identified SNPs at the *FTO* or *FGF21* loci, which may be relevant for protein intake. For instance Chu et al. (41) showed no significant evidence for an association between rs10163409 at the *FTO* locus and protein intake ( $\beta = -0.05\%E$ ;  $P = 0.08$ ), whereas Tanaka et al. (14) showed a significantly positive association between rs1421085, which was not in LD to rs10163409, and protein intake ( $\beta = 0.08$ ;  $P \leq 0.001$ ). However, due to the exclusion of protein intake for this review, the article gained more focus and clarity.

The search strategy might be also biased due to the inclusion of selected gene names. It is assumed that this had no impact on the results, because the *MC4R* locus—not included in the list of search terms—was identified as the second most common locus published for the reviewed topic.

A limitation is the high heterogeneity of data due to sample size, nutritional assessment, and characteristics of participants. The FFQ is the most commonly used dietary assessment tool to represent energy intake in observational studies. As mentioned by Cade et al. (65), FFQs may poorly represent dietary intake, which can lead to both

overestimation and underestimation of macronutrient intake. It could be speculated that there is a relation between the assessment tool used for dietary intake as well as the study type and the significance level of the results. As shown in Tables 1–3, there was no tendency for such bias.

Studies also varied in the statistical analysis and in the definition of the primary endpoints. In nutrition research, the comparison of results across studies and the replication of valid data is a major area of concern. There is an urgent need for studies harmonizing the data on macronutrient intake between the cohorts and standardizing the applied statistical models.

Due to large differences in the primary outcomes, a formal quality assessment was not performed. In addition, data pooling and performing a meta-analysis were not considered to be appropriate, because the data were too heterogeneous for statistical pooling. Therefore, a narrative synthesis as indicated in PROSPERO was conducted. A general limitation, especially in the field of genetic association studies, was the high publication bias (66). There is strong evidence that negative results are less frequently published.

The “pleiotropic” effect of identified SNPs may show the complexity as well as the challenge of gene-based dietary recommendations. Most of the genetic loci identified in this systematic literature search represent candidate genes (e.g., *PPARG*) for biological phenotypes. Only a few SNPs investigated for an association with total energy, carbohydrate, or fat intakes have been identified as BMI-related SNPs in GWASs (7, 13, 62). Tanaka et al. (14) (Supplemental Table 1) identified some loci being associated with macronutrient intake, whereas most of these associations were not confirmed by replication analysis. Another weakness is that prospective intervention studies are needed for confirmation before any conclusion on the clinical relevance can be drawn. In addition, the small effect size of the SNPs identified and potential gene-gene interactions may require studies focusing on genetic scores.

### Conclusions

The present review searched systematically for associations between SNPs and total energy, carbohydrate, and fat intakes. The principal finding was that the current literature does not provide evidence for consistent associations between SNPs and total energy, carbohydrate, or fat intakes. Therefore, the conclusion is that the current knowledge is too limited to derive dietary advice for weight management on the basis of genetic information. More efforts and clinical trials are needed to understand the mechanisms behind genetic variants and how they may interact with the lifestyle and environment.

### Acknowledgments

We thank Stefanie Brunner for providing methodologic advice. Furthermore, we are grateful to Lynne Stecher for proofreading the manuscript. In addition, we thank Amway GmbH, Puchheim, Germany for financial support. All authors read and approved the final manuscript.

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